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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,694	10/07/2003	Benjamin Lewis Margolis	034536-0839	3575

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/679,694	MARGOLIS, BENJAMIN LEWIS	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 47-50 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 47-50 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 07 October 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/12/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-46 were canceled. Claims 47-50 were added. Clams 47-50 are pending and examined on the merits.

Claim Rejections - 35 USC § 112

2. Claims 47-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for prognosis of breast cancer, wherein the concentration of either Her-2 or GRB-7 (specific components of a specific tyrosine kinase polypeptide/adaptor polypeptide complex) is determined and correlated to a prognosis, wherein elevated levels of either Her-2 and GRB-7 indicate a poor prognosis, does not reasonably provide enablement for methods of prognosis of a broad scope of "oncogenic disorders involving a receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex", wherein differences compared to levels of any component of any tyrosine kinase polypeptide/adaptor polypeptide complex found in a normal tissue are correlated with either a good prognosis or a poor prognosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is that the full scope of the claims is not enabled by the specification.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the

relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The claims are broadly drawn to methods of prognostic evaluation of a patient suspected of having an oncogenic disorder. The breadth of the claims is also found in the measurement steps of the method, where the concentration of any component of any tyrosine kinase polypeptide/adaptor polypeptide complex is measured. Furthermore, the claims are broad because the correlation step relates the measurements to any prognosis. A prognosis may be good, poor, or may be related to response various therapies. For example, Her-2 levels correlate with a poor response to endocrine or alkylating agent therapies in breast cancer, but is a positive predictive factor for anthracycline therapy in breast cancer (see Yamauchi, H. et al. J. Clinical Oncology, 19(8): 2334-2356, 2001; see abstract). As the claims are broadly recited, any change in levels of any component of any tyrosine kinase polypeptide/adaptor polypeptide complex is related to any prognosis.

The specification narrowly provides guidance with respect to a specific tyrosine kinase polypeptide/adaptor polypeptide complex, that of the Her-2/GRB-7 complex, and shows that increases in concentration levels of GRB-7 are correlated with increases in concentrations of Her-2, a known prognostic indicator for breast cancer. Therefore, the guidance provided by the specification is not commensurate in scope with the broad scope of the claims.

The art of using specific protein levels of tyrosine kinases for the prognosis of cancer is not a predictable field, i.e. the levels of specific protein may correlate with a poor prognosis in one type of cancer, but not be predictive of outcome in a second type of cancer. In the case of Her-2, high concentrations of Her-2 correlate with a poor prognosis in patients with breast

cancer, but this is not the case in urinary bladder cancer (see Lee, S.E. et al, Anticancer Res. (1994) 14(3B): 1317-1324, Abstract only) or in non-small-cell lung cancer (see Pfeiffer, P. et al, Br. J. Cancer (1996) 74(1): 86-91, Abstract only). Therefore, a demonstration of a correlation between GRB-7 levels and a poor prognosis in breast cancer cannot be readily extrapolated to methods where any component of a tyrosine kinase polypeptide/adaptor polypeptide complex is correlated to any type of cancer or even, more narrowly, where levels of GRB-7 are correlated to a prognosis for any type of cancer.

Because of the breadth of the claims in contrast to the narrow teachings of the specification in combination with the unpredictability of the tumor markers to correlate with cancer prognosis, one of skill in the art would have to engage in further experimentation to practice the full scope of the claimed inventions. This further experimentation would be undue experimentation because there would not be an expectation of success, as the experiments would be to discover whether or not the outcome or response to therapy of a particular cancer correlated with a component of a tyrosine kinase polypeptide/adaptor polypeptide complex.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 47-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Nugent (Nugent, A. et al., Clinical Chemistry 38(8, Pt. 1): 1471-1474, 1992).

Claims 47-50 are drawn to method for prognostic evaluation of a patient suspected of exhibiting an oncogenic disorder involving a receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex comprising determining the concentration of a component of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex present in a biological sample, comparing the concentration of the component to the concentration range of the component of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex known to be present in normal tissue of the same type as present in the biological sample and correlating the result to a prognosis.

All of the claims read on methods of prognostication based on measurement of c-erbB-2 protein (Her-2), which is a component of the exemplified "receptor protein tyrosine kinase polypeptide/adaptor polypeptide, i.e. Her-2/GRB-7 complex. Claim 50 also reads on methods based on measurement of c-erbB-2 protein (Her-2), because although the phrase "wherein the adaptor protein polypeptide is a GRB-7 polypeptide, the claim does not contain the positive recitation that the component measured is GRB-7 polypeptide.

Nugent teaches a method of measuring and comparing concentrations of c-erbB-2 in samples of breast tissue or benign breast tumor. Nugent teaches that an elevation of c-erbB-2 protein concentration is a prognostic marker for breast cancer, with higher levels of c-erbB-2 found in cancers with a poor prognosis. Therefore, Nugent teaches the claimed methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over unpatentable over Margolis (Margolis, B. et al., J. Cell Biochem., Abstract, Supplement 18B, Feb. 1994, page 241; cited in the IDS) in view of Nugent (supra).

Margolis teaches that GRB-7 is amplified and overexpressed in concert with Her-2 in breast cancer cell lines and tissue from breast cancer patients. Margolis teaches that GRB-7 binds tightly to Her-2 via its SH2 domain,and that almost all of the phorphorylated Her-2 is

bound by GRB-7. Therefore, Margolis teaches a correlation between concentrations of Her-2 (a known prognostic indicator) and concentrations of GRB-7). Margolis fails to explicitly teach a method for prognosis in breast cancer patients comprising the determination of GRB-7 concentrations. However, Nugent teaches that concentrations of Her-2 are correlated with a poor prognosis in breast cancer patients. Because Margolis teaches that there is a close correlation between GRB-7 concentrations and Her-2 concentrations and because almost all of the phosphorylated Her-2 is bound by GRB-7, it would have been prima facie obvious to one of ordinary skill in the art at the time the inventions was made to have used a method based on measurement of GRB-7 concentrations for determining the prognosis of breast cancer in patients. One would have been motivated to have used GRB-7 as a marker of poor prognosis because of its very close correlation with levels of Her-2, which is a marker of poor prognosis in breast cancer.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the

status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
June 19, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER